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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/766,535	LE ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date Apr 16, 2004
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 and 3 have been amended. Claims 4-10 have been added. Claims 1-10 are pending and under consideration. The claims are examined to the extent that they read on the elected species of multiple sclerosis.

Text of sections of Title 35, US Code not found in this action can be found in a prior action.

The rejection of claims 1-3 under 35 U.S.C. 103(a) as being unpatentable over Beck et al (Acta Neurologica Scandinavica, 1988 Oct, Vol. 78, pp. 318-323) in view of the abstract of Beck et al (Immunobiology, 1987, Vol. 175, pp. 91-92) and the abstract of Selmaj et al (Neuroimmunology, 1987, Vol. 16, page 159) is maintained for reasons of record. Claim 10 is also rejected for the same reasons of record as many murine anti-TNF antibodies are produced by hybridoma technology.

Claim 1 is drawn to a method for treating TNF-mediated a neurodegenerative disease in a human comprising administering at least one anti-TNF monoclonal antibody or a TNF-binding fragment thereof. Claim 2 embodies the method of claim 1 wherein the TNF-mediated neurodegenerative disease is multiple sclerosis. Claim 3 is drawn in part to the method of claim 1 wherein the TNF-mediated disease is multiple sclerosis.

Beck et al teach that levels of TNF increase in multiple sclerosis patients preceding clinical symptoms, and that in patients with chronic progressive disease, levels of TNF were elevated between exacerbations (abstract and page 322, under the heading "TNF production"). Beck et al suggests that increased levels of TNF before exacerbations play a pathogenic role in multiple sclerosis, and compare the levels or circulating TNF alpha in mice with cerebral malaria. Beck et al teach that said mice can be protected from the pathogenic effects of cerebral malaria by anti-TNF alpha antibodies (pages 322-323, bridging paragraph). Beck et al further suggest that TNF may play a role in maintaining the chronic progressive and invalidating forms of multiple sclerosis (final paragraph).

The abstract of Beck et al teaches that the TNF produced during acute exacerbations of multiple sclerosis was completely neutralized by anti-TNF antibodies.

The abstract of Selmaj et al teaches that a culture of spinal cord tissue contacted with TNF alpha resulted in swelling of the myelin sheaths along the affected fibers. electron microscopy revealed that the swelling appeared to result from an influx of water into the periaxonal space which led to myelin breakdown.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to treat human multiple sclerosis by the administration of an anti-TNF alpha antibody. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Beck et al regarding the correlation between TNF levels and exacerbations in multiple sclerosis patients, and the correlation between progressive multiple sclerosis and increased levels of TNF between exacerbations, in addition to the teachings of Beck et al regarding the protective effect of anti-TNF alpha antibodies in mice suffering from cerebral malaria; the teaching of the abstract of Beck et al which identify the elevated levels of TNF in multiple sclerosis patients specifically as TNF alpha; and the teachings of the abstract of Selmaj et al on the ability of TNF to induce damage directly on nerve cells in culture . One of skill in the art would recognize that episodes of acute elevated TNF production and well as chronically elevated levels of TNF in the brains of multiple sclerosis patients was responsible for myelin breakdown and further progression of the disease. Therefore on of skill in the art would be motivated to reduce the levels of TNF in said patients by means of binding to an anti-TNF antibody. One of skill in the art would recognize that binding to the anti-TNF antibody was effective at protecting mice from the pathological effects of cerebral malaria and therefore if would be reasonable to conclude that anti-TNF antibodies would protect humans from the pathological effects of multiple sclerosis, because both multiple sclerosis and cerebral malaria are mediated by elevated levels of TNF alpha.

Applicant argues that the rejection is faulty because applicants method is directed to methods of treatment not prevention. this has been considered but not found persuasive. IT is noted by the teachings of Beck et al (1988) that multiple sclerosis is a

chronic disease punctuated by episodes of acute episodes. Thus the treatment of patients having ms between episodes of acute disease would be considered as a method of treatment. Applicant argues that the disclosure of Beck on elevated levels of circulating TNF alpha in mice with cerebral malaria is irrelevant to the instant invention which is directed to the treatment of ms. This has been considered but not found persuasive., The fact that anti-TNF antibodies can protect mice from the pathological condition resulting from elevated levels of cerebral malaria is relevant to the instant invention, as elevated levels of TNF are associated with exacerbations of ms as taught by Beck et al;. Thus it would be expected that the ms patient having acute symptoms of MS, or an MS patient in between acute episodes of MS would benefit from anti-TNF antibodies.

Applicant argues that the disclosure in the abstract of Selmaj et al regarding the effect of TNF on nerve cultures are not relevant to the instant invention because the disclosure is speculative stating TNF may involve an ion channel effect and suggest only that soluble factors are involved with demyleination. Applicant states that the TNF effect on nerve tissue was not reversible. this has been considered but not found persuasive. Regarding the irreversibility of the TNF effect, one of skill in the art would expect that nerves damaged in vivo would not regenerate, and thus it would not be expected that the damaging effects of TNF alpha would be reversible. Regarding the ion channel effect of TNF on nerve cultures, it is noted that this detail was not relied upon for the instant rejection, only the pathological effect of the TNF on the nerve culture need be observed. Regarding the suggestion that soluble factors may be involved in demylination, it is especially of note that cultures of nervous tissue with interferon gamma or IL-2 did not exhibit damage to the cultured nervous tissue.

Applicant argues that the claimed methods show unexpected results in light of the teachings of the prior art that indicate that diseases mediated by overlapping effects of cytokines would not necessarily benefit from targeting one specific cytokine. This has been considered but not found persuasive. in light of the abstract of Selmaj et al which teaches that only TNF alpha but not INF gamma nor IL-2 mediated damage of nervous tissue explants.

Applicant argues that the instability and lack of specificity of the prior art antibodies could not exert the therapeutic efficacy required in the instant claimed methods. this has been considered but not found persuasive. Only claims 4-7include limitations of the specific antibody disclosed in the instant specification.

Claims 1-3, 4, 7, 8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beck et al (Acta Neurologica Scandinavica, 1988 Oct, Vol. 78, pp. 318-323), the abstract of Beck et al (Immunobiology, 1987, Vol. 175, pp. 91-92) and the abstract of Selmaj et al (Neuroimmunology, 1987, Vol. 16, page 159) as applied to claims 1-3 above, and further in view of Moller et al (Cytokine 1990, Vol. 2, pp. 162-169, cited in a related application).

The specific embodiments of claims 1-3 and 10 are set forth above. Claim 4 embodies the method of claim 1 wherein the anti-TNF antibody competitively inhibits binding of TNF to cA2. Claim 7 embodies the method of claim 1 wherein a single or divided dose of anti-TNF antibody from 0.1 to 100 mg/kg is administered to a human to treat the neurodegenerative disease of ms. Claim 8 embodies the method of claim 1 wherein the antibody neutralizes human TNF-alpha in vivo. Claim 10 embodies the method of claim 1 wherein the antibody is produced by a method using a hybridoma.

The teachings of Beck et al (Acta Neurologica Scandinavica, 1988 Oct, Vol. 78, pp. 318-323), the abstract of Beck et al (Immunobiology, 1987, Vol. 175, pp. 91-92) and the abstract of Selmaj et al (Neuroimmunology, 1987, Vol. 16, page 159) which render obvious instant claims 1-3 and 10 are set forth above. The combination of references do not render obvious an anti-TNF antibody with the claimed characteristics of claims 4, 7, and 8.

Moller et al teach the mAb195 which specifically binds TNF from humans and chimpanzees, but which does not bind to mouse, rat, rabbit, dog or pig TNF (Table 2). The instant specification describes A2 as binding to human and chimpanzee TNF but not binding to mouse, rat, rabbit, dog or pig TNFalpha (page 87, lines 28-35). Thus, it appears that the instant A2 and chimerized A2 bind to the same or a overlapping epitope as mAb195, and therefore would compete for binding to TNF with A2 and cA2. Moller

et al teach that mAb195 can bind to TNF alpha when TNF alpha was bound to the TNF receptor and that this suggests an alternative mechanism for the neutralization of the biological activity of TNF-alpha by the mAb195 antibody which does not involve the blocking of the binding of TNF alpha to its receptor. Moller et al discriminates between receptor binding epitopes of TNF alpha and neutralization epitopes of TNF alpha (page 166, first column, lines 13-22).

It would have been prima facie obvious to use the anti-TNF antibody of Moller et al to neutralize human TNF in vivo. One of skill in the art would have been motivated to do so by the teachings of Beck on the neutralization of TNF by anti-TNF antibodies in mice for the protection of said mice from the pathological effects resulting from elevated levels of TNF in cerebral malaria. One of skill in the art would be motivated to use an anti-TNF alpha antibody which neutralized human TNF alpha in vivo in order to treat ms.

With regard to the limitations of the dose range of claim 7, it is noted that the optimization of a dosage range is within the purview of one of skill in the art.

Claims 1-5 and 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beck et al (Acta Neurologica Scandinavica, 1988 Oct, Vol. 78, pp. 318-323), the abstract of Beck et al (Immunobiology, 1987, Vol. 175, pp. 91-92) the abstract of Selmaj et al (Neuroimmunology, 1987, Vol. 16, page 159) and of Moller et al (Cytokine 1990, Vol. 2, pp. 162-169, cited in a related application) as applied to claims 1-3, 4, 7, 8 and 10 above, and further in view of. Zerler (EP 380,068, cited in a related application).

Moller et al teach the murine mAb 195 (page 163, first column under "Production of Monoclonal Antibodies" which specifically binds to an epitope of TNF alpha that is present on human TNF alpha and Chimpanzee TNF alpha and does not show any cross-reactivity with other human proteins including TNF-beta (page 164, second column under the heading "Characterization of Monoclonal antibodies by Immunoblot" and page 165 first column, lines 3-5). Moller et al teach that mAb 195 neutralized the cytotoxic activity of human TNF alpha in vitro (page 164, first column and Table 2, second column). Moller et al also teach that administration of the mAb 195 to mice injected with human TNF alpha blocked the lethal effect of TNF in the mice (page 165, second

column, under the heading "Neutralization of Human TNF Alpha in the Mouse"). Thus, Moller et al teach a murine antibody which specifically binds to an epitope of human TNF alpha, wherein said antibody is a high affinity murine monoclonal antibody (defined as by the ability to block the activity of THF alpha in vitro, and the inhibition of a pathological activity of TNF alpha (TNF-induced lethality), the neutralization of TNF alpha under physiological conditions (within the mouse). Moller et al do not teach a chimeric antibody comprising part of a human constant region, nor a human IgG1 constant region.

Zerler et al teach a chimeric antibody comprising part of a human constant region derived from murine antibodies which bind to the Il-2 receptor. Zerler et al teach a general method for how to make recombinant chimeric antibodies comprising a IgG1 human constant regions (page 5, lines 53-55) and murine variable regions. Zerler et al suggest that chimeric antibodies against TNF can be made in a similar method (page 10, line 55 to page 11, line 8). Zerler et al teach the expression of the vector encoding the chimeric antibodies in mammalian cell lines transformed by said vector (claim 13). Moller et al do not teach a chimeric antibody based on mAb195.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to make a chimeric antibody having a IgG1 constant region, wherein the variable region was derived from mAb195. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Zerler et al regarding the advantages of chimeric antibodies versus murine antibodies such as the elimination of allergic side effects and the increase in serum half live (page 3, lines 29-33), and the suggestion of Zerler et al, that the disclosed methods of making the recombinant chimeric antibodies could be applied to antibodies against TNF. Zerler et al specifically teach that an antibody having a human IgG1 constant region has a serum half-life of 21-23 whereas a murine antibody has a serum half life of 15-16 hours.

Claim 6 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.

7/12/2004

KAREN A. CANELLA PH.D
PRIMARY EXAMINER